REMARKS/ARGUMENTS

The Invention

The invention pertains to a composition comprising an interleukin-2 receptor associated polypeptide (ILRAP), wherein the polypeptide is capable of forming a complex with the monoclonal antibody produced by the hybridoma PTA-82, and methods of purifying the same.

The Pending Claims

Claims 1, 3, 5, 9, 11-15, 23, and 26-29 are pending. Claims 1, 3, 5, 23, and 26-29 are directed to compositions comprising interleukin-2 receptor associated polypeptides, which are capable of forming a complex with monoclonal antibodies produced by the hybridoma PTA-82, wherein said interleukin-2 receptor associated polypeptides are expressed by cells selected from the group consisting of Kit-225 cells and YT cells. Claims 9 and 11-15 are directed to methods of purifying said interleukin-2 receptor associated polypeptides. Claim 9 has been amended to clarify the identity of the recited interleukin-2 receptor associated polypeptides. The amendment is supported throughout the specification as filed, e.g., at page 26, line 7, to page 28, line 17.

Discussion of Rejection under 35 U.S.C. § 112, first paragraph

Claims 1, 3, 5, 9, 11-15, 23 and 26-29 remain rejected under 35 U.S.C. § 112, first paragraph, as allegedly not enabled for the reasons of record set forth in the Office Action mailed on June 16, 2006 ("the June 16, 2006 Office Action"), the Advisory action mailed November 1, 2006 ("the Advisory Action"), and the Office Action mailed on August 23, 2007 ("the August 23 Office Action"). Applicants respectfully traverse.

Applicants respectfully submit that the Office appears to have misunderstood Applicants' arguments and, therefore, mischaracterizes Applicants' position. In particular, the Office incorrectly states that Applicants have indicated

> that anti-Tac did co-IP the claimed ILRAPs, and it just did not co-IP enough of the claimed ILRAPs to be visualized in the SDS-PAGE, indicating the association of the claimed ILRAPs with IL-2R

(Offica Action, page 3, emphasis added). Contrary to what is stated by the Office, however, Applicants have consistently argued the opposite (as demonstrated by the experimental evidence). For example, Applicants' Reply to the August 23 Office Action states:

> the Office has provided no basis for contradicting Applicants actual data showing that using anti-Tac to pull down IL-2R, does not pull down enough (if any) of the claimed ILRAP so as to be identifiable by SDS-PAGE (the March 2006 Waldmann Declaration, Exhibit 3)

(Reply to Office Action filed December 21, 2007, ("Reply of December 21, 2007") page 6, first full paragraph, emphasis added). Thus, Applicants have not argued that anti-Tac and ILRAPS can significantly co-IP because there is no experimental evidence of such co-IP.

For clarity, Applicants provide the following summary of what they understand to be the Office's concerns regarding enablement and Applicants' responses thereto.

First Issue: The Office has questioned whether or not the claimed ILRAPs associate with IL-2R because, according to the Office, "it is not explainable that 5F7 antibody is able to co-precipitate the IL-2R...but the reverse is not true, i.e., anti-Tac is not able to co-precipitate the ILRAPs" (November 1, 2006 Advisory Action, page 2, second full paragraph, emphasis added). However, Applicants have explained that this assertion is based on an untenable assumption, namely, that if anti-Tac binds IL-2R and ILRAP associates with IL-2R, then an IP with anti-Tac must co-IP all ILRAPs.

As a general matter, the foregoing assumption is not always sound. There is no reason for assuming, as a general principle, that a monoclonal antibody (such as anti-Tac) must co-IP every protein associated with the antigen, such that every associated protein can be visualized by SDS-PAGE. For example, if antibody binding displaces or prevents binding by an associated protein, there would be nothing surprising about the inability of the antibody to co-IP the associated protein. In any case, except for this unsupported assumption, the Office has provided no basis for contradicting Applicants' actual data, which show that using anti-Tac to pull down IL-2R, does not pull down (or does not pull down enough of) the claimed ILRAP so as to be identifiable by SDS-PAGE (the March 2006 Waldmann Declaration, Exhibit 3).

Moreover, Applicants' data consistently indicate that anti-Tac pulls down a relatively large amount of IL-2R, whereas 5F7 antibody pulls down a relatively small amount of IL-2R. This difference in amounts of IL-2R that is pulled down is clearly shown in the strong 55 kDa band in lane 2 (the large pool of IL-2R pulled down with anti-Tac IP) and the weaker 55 kDa band in lane 3 (the small pool of IL-2R pulled down by co-IP with 5F7) of Exhibit 3 in the March 2006 Waldmann Declaration. For its part, the Specification also states that extended exposure was required to visualize the 55 kDa polypeptide band (IL-2R) pulled down by anti-ILRAP in Fig. 4 (Specification, page 8, lines 1-4). Thus, Applicants data consistently indicate the amount of IL-2R interacting with ILRAP (under IP conditions) represents only a fraction of the total amount of IL-2R that can be pulled down using the anti-Tac monoclonal antibody, which was specifically raised against IL-2R. Therefore, the absence of ILRAP in lane 2 of Exhibit 3 is readily explainable: the amount of IL-2R interacting with ILRAP (under IP conditions) is so much smaller than the total amount of IL-2R pulled down with anti-Tac that IP of IL-2R with anti-Tac does not co-IP (or does not co-IP enough of) the claimed ILRAPs; and, thus, the ILRAPs are not detectable in the SDS-PAGE of Exhibit 3.

Alternatively or relatedly, the claimed ILRAPs may be displaced by anti-Tac during IP. In either case, Applicants have presented the Examiner with data that is consistent and explainable. The Office, on the other hand, has not presented a reason or basis for contradicting the actual experimental data.

Second Issue: The Office has questioned whether or not the claimed ILRAPs associate with IL-2R because "there is no direct evidence in the Specification showing the direct association between the claimed ILRAPs and the IL-2R" (November 1, 2006 Advisory Action, page 2, second full paragraph). The Specification, however, directly contradicts this contention. The Specification reports that when Applicants pre-cleared cell lysates with anti-Tac conjugated beads, the 55 kDa band that co-immunoprecipitated with the claimed ILRAPs in Fig. 4 was reduced and was no longer visible (Specification, page 8, lines 6-9). Accordingly, there is direct evidence in Applicants' Specification that some, if not all, of the 55 kDa can be depleted using anti-Tac.[1] Additionally, Example 5 of the Specification reports that addition of IL-2 caused ILRAP to be internalized with IL-2Rβ in Kit-225 cells at 37 °C

[1] As explained more fully below, evidence that anti-Tac reduces IL-2R that co-IPs with anti-ILRAP does not contradict evidence that anti-Tac fails to co-IP ILRAP (or enough ILRAP to be visualized by SDS-PAGE).

(Specification, page 33, line 11-21; and page 38, lines 5-17). In contrast, ILRAP levels did not change when IL-2 was added to Kit-225 cells at 4 °C, a temperature at which IL-2R internalization is blocked (Specification, page 38, lines 5-17). Example 6 of the Specification reports that flow cytometric resonance energy transfer (FRET) verified that ILRAP and IL-2Rα are associated on the surface of T-cell lines (Specification, page 39, lines 3-5, and Figure 5). Thus, Applicants respectfully submit that the Specification provides uncontradicted evidence that ILRAP interacts with IL-2R.

Third Issue: The Office contends that Applicants are arguing two mutually exclusive positions (Office Action, page 3). This contention is based, at least in part, on the Office's view that Applicants have argued that anti-Tac did co-IP the claimed ILRAPs to be visualized under co-IP conditions described by applicants. However, Applicants have clearly and consistently argued, based on experimental evidence, that anti-Tac does not co-IP (or does not co-IP enough of) the claimed ILRAPs under the conditions described by Applicants, such that the claimed ILRAP are not visualized by SDS-PAGE analysis of IP with anti-Tac. As detailed more fully above in the "First Issue" discussion, absence of detectable ILRAP is explainable, for example, by (i) anti-Tac displacing or preventing ILRAP binding to IL-2R and/or (ii) ILRAP not binding (or binding to a such a small pool or subset of) the IL-2R that is reactive to anti-Tac under IP conditions, such that ILRAP is not detectable by SDS-PAGE after IP with anti-Tac.

Other evidence in the specification showing that pre-clearing cell lysates with anti-Tac reduced the amount of 55 kDa that can co-IP with anti-ILRAP (thus providing direct evidence that the ILRAPS associate with IL-2R), does not undermine Applicant's arguments or the experimental evidence presented in the March 2006 Waldmann Declaration. Evidence that anti-Tac depletes the relatively small pool of IL-2R that associates with ILRAP does not contradict Applicants' evidence that anti-Tac does not co-IP ILRAP (or enough ILRAP to be visualized by SDS-PAGE). Anti-Tac is specific to IL-2R and thus should reduce the IL-2R available for co-IP with all associated proteins, including those that, like ILRAP, associate with a relatively small pool of IL-2R (as compared to total IL-2R). Moreover, such depletion should also be expected if there is binding site or other steric competition between ILRAP and anti-Tac, since anti-Tac may prevent IL-2R association with ILRAP and subsequent co-IP with anti-ILRAP.

Fourth Issue: Claim 9 stands rejected for allegedly insufficiently specifying the identity of the recited ILRAPs. Although Applicants disagree with the rejection, the claim has been amended to specify that the recited ILRAPs are capable of forming a complex with the monoclonal antibody produced by the hybridoma PTA-82. The amendment clarifies that the recited ILRAPs are not distinct from what is disclosed in the specification.

In view of the reasons presented herein, Applicants respectfully request withdrawal of the rejection under 35 U.S.C. § 112, first paragraph, as to claims 1, 3, 5, 9, 11-15, 23 and 26-29.

Discussion of Rejection under 35 U.S.C. §§ 102(b) or 103(a)

Claims 1, 3, 5, 9, 11-15, 23 and 26-29 remain rejected under 35 U.S.C. § 102(b) as being anticipated by, or, in the alternative, under 35 U.S.C. § 103(a) as obvious over Colamonici et al., *J. Immunol.*, 145:155-160 (1990) ("Colamonici"), for the same reasons set forth in the previous Office Actions mailed June 3, 2004, April 19, 2005, October 18, 2005, June 16, 2006, and November 1, 2006. Applicants respectfully traverse.

The prior art rejection repeats the same arguments discussed above for the enablement rejection. Contrary to what is stated by the Office, however, Applicants have not argued that anti-Tac did co-IP the claimed ILRAP (Office Action, page 5). Instead, Applicants have consistently argued that they have provided the Office with "actual data showing that using anti-Tac to pull down IL-2R, does not pull down enough (if any) of the claimed ILRAP so as to be identifiable by SDS-PAGE." (See Reply of December 21, 2007, page 6, first full paragraph, emphasis added).

The prior art rejection also states that the arguments in Applicants' Reply of December 21, 2007 "focus on criticizing the prior art reference and without providing further supporting evidence that the claimed ILRAPs are distinct from the prior art by Colamonici" (Office Action, page 5). However, Applicants respectfully submit that their argument is not based on a criticism of Colamonici. On the contrary, Applicants arguments have focused on the experimental evidence of record showing that the claims differ from what is disclosed in Colamonici.

Such evidence that the claims differ from what is disclosed in Colamonici has been provided by way of the March 17, 2006 Declaration under 37 C.F.R. § 1.132 ("the March 2006 Waldmann Declaration"). Exhibit 1 to the March 2006 Waldmann Declaration shows that the polypeptide precipitated from MT-1 cells using anti-ILRAP antibody 5F7 (lane 2) migrates below the 37 kDa polypeptide precipitated using anti-Tac (lane 3). Colamonici specifically reports that the relevant 37 and 20 kDa polypeptides cited by the Examiner were precipitated from MT-1 cells using anti-Tac (page 159, second column, second paragraph). Moreover, since the analysis of Exhibit 1 to the March 2006 Waldmann Declaration was done in the same SDS-PAGE gel, the observed difference in migration cannot be attributed to variations in gel concentrations and running time. Accordingly, the March 2006 Waldmann Declaration establishes that there is a size difference between the claimed polypeptide and that disclosed in Colamonici.

However, the June 16, 2006, Office Action and November 1, 2006, Advisory Action dismiss Applicants actual experimental evidence regarding size difference because, according to the Office,

> the rejection is based on Colamonici's teachings of Hut-102 cells, not MT-1 cells as the presently claimed polypeptides are from Hut-102 cells or Kit-225 cells. Although Colamonici teaches that the 37 and 20 kDa bands also appeared in MT-1 cells, it is unclear if they are the same molecules as that in 102 cells, which are also disclosed by Colamonici.... Merely the same MW does not automatically indicate that they are the same molecules, especially given ... different cell sources."

(June 16, 2006, Office Action, page 3, second paragraph). Inexplicably, the Office rejects the explicit teachings in Colamonici that the 37 and 20 kDa polypeptides seen in Hut-102 cells are the same as those in MT-1 cells because "[merely] the same MW does not automatically indicate that they are the same molecule." Thus, without experimental evidence or support in the art, the Office has taken the position that the Colamonici authors are incorrect. Without experimental evidence or support in the art, the Office disregards the statements in Colamonici that the 37 and 20 kDa bands in MT-1 and HUT-102 cells have the same size, have the same cellular and immunochemical properties, and were obtained in the same way, i.e., by surface labeling with ^{125}I-rIL-2 and co-immunoprecipitating with specific IL-2R antibodies (Colamonici, page 159, second column, second paragraph).

Applicants have taken Colamonici at its word, used the same antibody and cell lines disclosed in Colamonici, and have shown that the 37 kDa peptide pulled down with anti-Tac differs in size from what the claimed polypeptide pulled down with Applicant's 5F7 antibody. Without any experimental evidence or support in the art, the explicit teachings in Colamonici do not support the prior art rejection.

The Office Action also states that the rejection "is based on applicants data, which do not show a clear distinctness between the claimed ILRAPs and that of Colamonici. Further, the only evidence that the present invention depends on is the 'difference' in MW" (page 5). Applicants respectfully disagree for the following reasons.

Exhibit 4 of the March 2006 Waldmann Declaration demonstrates that, whereas the claimed ILRAP is clearly detectable on the surface of Kit 225 cells, the claimed ILRAP is not detectable by flow cytometry on the surface of MLA-144 cells (see also Item 9 of the March 2006 Waldmann Declaration). Colamonici, on the other hand, specifically teaches that the prior art 37 kDa peptide was detectable on the surface of intact MLA-144 cells (see page 159, second column, second paragraph, and Figure 5). Accordingly, Applicants have shown that the claimed polypeptide differs from the prior art by more than MW. Applicants have also shown that the claimed polypeptide differs from the prior art according to expression patterns in different cells. The claimed polypeptide is not expressed on the surface of MLA-144 cells and thus clearly differs from what is disclosed in Colamonici.

Applicants have provided clear evidence that the claimed polypeptide is not expressed in MLA-144, in contrast to the polypeptide of Colamonici. Therefore, applicants submit that there is nothing "indecisive" about the evidence showing that the claimed polypeptide differs from what is disclosed in the prior art.

Moreover, applicants submit that the Office has not presented a prima facie case by asserting that the differences between the prior art and the claimed invention "could be explained by experimental deviation" (Office Action, page 6). The assertion is conclusory and unsupported. In contrast, Applicants have provided evidence of differences in MW *in the same SDS PAGE* gel, which is based on experimental data. Applicants have also used an antibody that is specific to the claimed polypeptides to demonstrate by flow cytometry that the claimed polypeptide is absent from the surface of MLA-144 cells. Colamonici explicitly

teaches that the relevant prior art polypeptide is found on the surface of MLA-144. The Office has not provided any convincing rationale for doubting that Applicant's evidence establishes that the claimed polypeptides differ from the 37 and 20 kDa bands taught in Colamonici.

For the reasons presented herein, Applicants respectfully submit that the prior art does not disclose (either alone or in any combination identified by the Office) each and every element of the claimed polypeptides. Therefore, Applicants respectfully request withdrawal of the present rejection under 35 U.S.C. §§ 102(b) or 103(a).

Conclusion

In view of the foregoing reasons, this application is considered in good and proper form for allowance, and the Examiner is respectfully requested to pass this application to issue. If, in the opinion of the Examiner, a telephone conference would expedite the prosecution of the subject application, the Examiner is invited to call the undersigned attorney.

Respectfully submitted,

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Date: July 15, 2008